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Serum vitamin D and risk of bladder cancer in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial

Alison M. Mondul¹, Stephanie J. Weinstein¹, Ron L. Horst², Mark Purdue³, and Demetrius Albanes¹

¹Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Department of Health and Human Services, Bethesda, Maryland

²Heartland Assays, Inc., Ames, Iowa ³Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Department of Health and Human Services, Bethesda, Maryland

Abstract

Background—The one previous prospective study of vitamin D status and risk of urinary bladder cancer found that male smokers with low serum 25-hydroxy-vitamin D (25(OH)D) were at a nearly 2-fold increased risk. We conducted an analysis of serum 25(OH)D and risk of bladder cancer in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Study, and examined whether serum vitamin D binding protein (DBP) concentration confounded or modified the association.

Methods—375 cases of bladder cancer were matched 1:1 with controls based on age (+/- 5 years), race, sex, and date of blood collection (+/- 30 days). Conditional logistic regression was used to estimate odds ratios and 95% confidence intervals of bladder cancer by pre-diagnosis levels of 25(OH)D.

Results—We found no strong or statistically significant association between serum 25(OH)D and bladder cancer risk (Q1 vs. Q4: OR=0.84 95% CI=0.52–1.36; *p-trend* = 0.56). Further adjustment for serum DBP did not alter the findings, nor was there a main effect association between DBP and risk.

Conclusion—In contrast to the one previous study of this hypothesis, we observed no association between vitamin D status and risk of bladder cancer; this difference could be due to the inclusion of women and non-smokers in the current study population, or to differences in the distribution of vitamin D concentrations between the two study populations.

Impact—These findings may contribute to future meta-analyses and help elucidate whether the vitamin D-bladder cancer association varies across populations.

Keywords

Urinary bladder neoplasms; 25-hydroxyvitamin D; Case-control studies

Corresponding Author Contact: Alison M. Mondul, 6120 Executive Blvd. Ste. 320, Rockville MD, 21045, mondulam@mail.nih.gov, phone: (301) 496-5626, fax: (301) 496-6829.

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Introduction

Laboratory studies provide evidence that vitamin D promotes cell differentiation, and decreases cell proliferation, invasion, angiogenesis, and metastasis [1, 2]. Thus, it has been hypothesized that vitamin D may protect against cancer at multiple sites. Most epidemiologic evidence supports a protective association with colorectal cancer, but evidence concerning other cancers is inconsistent [1, 3]. For urinary bladder cancer, only one study has examined vitamin D status, as measured by serum 25-hydroxyvitamin D (25(OH)D) concentration, which showed that male smokers with low 25(OH)D had a nearly two-fold increased risk of bladder cancer compared to men with higher levels [4]. Further, few studies have examined the role of vitamin D binding protein (DBP), the major carrier of 25(OH)D in circulation, in the association between vitamin D and risk of cancer. We undertook an analysis of serum 25(OH)D and risk of bladder cancer in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Study, and examined whether serum DBP concentration confounded or modified the vitamin D association.

Methods

The PLCO Study has been described in detail previously [5]. Bladder cancer cases (n=369) with pre-diagnosis serum available occurred during 13 years of follow-up. Controls were sampled with replacement from PLCO Study participants who were alive and cancer free at the time the case was diagnosed and were matched 1:1 to cases on age (+/- 5 years), race, sex, and date of blood collection (+/- 30 days).

Details of the laboratory methods for measurement of 25(OH)D have been reported [6]. DBP was measured in the laboratory of Dr. William Kopp (SAIC-NCI, Frederick) by ELISA (R&D kits). Each batch contained four or six blinded quality control (QC) duplicates from four PLCO study participants. The range of inter- and intra-batch CVs across the four sets of duplicates were: 25(OH)D: 3.7-6.9% and 4.8-8.1%, respectively; DBP: 3.2-11.1% and 9.5-12.6%, respectively.

Conditional logistic regression was used to estimate odds ratios and 95% confidence intervals for bladder cancer by pre-diagnosis concentrations of 25(OH)D categorized as previously described [6]. We also examined quartiles of DBP as well as the molar ratio of 25(OH)D:DBP (an estimate of free circulating 25(OH)D) and risk of bladder cancer.

Models were conditioned on the matching factors. Multivariable models were further adjusted for smoking status (never, current, former), pack-years of smoking (continuous), dairy consumption (continuous), and use of aspirin or ibuprofen (yes/no).

Subgroup analyses were conducted stratifying by age (<64, ≥64 years), sex (male, female), race (white, non-white), smoking (never or former, current), season (sunnier: June-October, darker: November-May), study center (low UVB exposure latitude, moderate or high UVB exposure latitude) [7], and DBP (<median, ≥median). Interaction was assessed using the likelihood ratio test.

Results

Characteristics of cases and controls are shown in Table 1. We did not observe a strong association between serum 25(OH)D and bladder cancer (Table 2). An inverted U-shaped association was suggested, particularly when 25(OH)D was categorized as season-specific quartiles. This was attenuated with multivariable adjustment and was not statistically significant. Adjustment for serum DBP did not alter the findings, nor was DBP or the molar ratio of 25(OH)D:DBP associated with risk (Table 2). We observed no interaction between

25(OH)D and any of the following: age ($p=0.48$), smoking ($p=0.58$), sex ($p=0.51$), race ($p=0.56$), DBP ($p=0.64$), or study center UVB exposure ($p=0.28$). Restricting our analysis to current or former male smokers, an inverse association was suggested (vs. Q4; Q1:OR=1.26, 95%CI=0.67-2.36; Q2: OR=1.64, 95%CI=0.92-2.92; Q3: OR=1.42, 95%CI=0.80-2.53; $p\text{-trend}=0.34$).

Discussion

We found no evidence of an association between vitamin D and risk of bladder cancer. Neither adjustment for nor stratification by DBP changed the association with vitamin D. These results differ from those of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study of male smokers which found a protective association between vitamin D and bladder cancer risk [4]. This difference may be explained by the inclusion of women and non-smokers in the current analysis, as restricting the analysis to male smokers showed a modest inverse association. Although our study was sufficiently powered to detect an OR of 1.7 comparing the lowest to highest vitamin D quartile (i.e., higher risk similar in magnitude to that previously observed [4]), we did not have power to detect a weaker association, particularly in subgroups. Future studies should plan to examine differences in the association by gender and smoking status.

Importantly, the vitamin D distribution differs between the two cohorts; many PLCO participants were “replete” (25(OH)D 50-75 nmol/L; 41%) and few with 25(OH)D <25 nmol/L (5%). By contrast, given the population’s geographic location, the majority of the ATBC Study participants had 25(OH)D levels <50 nmol/L (64%), and many (45%) had levels <25 nmol/L. Additional studies in populations with a range of vitamin D distributions may help clarify the inconsistent findings from the two studies.

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Table 1

Selected baseline characteristics [medians (interquartile range) or number (percent)] for case and control subjects, PLCO Study

Characteristic	Controls (n=364)	Cases (n=369)	p-value
Age (years)	64 (61 – 67)	64 (60 – 68)	<i>matched</i>
Male	294 (80.8)	298 (80.8)	<i>matched</i>
Caucasian	344 (94.5)	348 (94.3)	<i>matched</i>
Height (cm)	178 (170 – 183)	175 (168 – 180)	0.19
Weight (kg)	84.7 (77.2 – 94.3)	83.2 (74.1 – 93.2)	0.12
BMI (kg/m ²)	27.2 (24.7 – 30.1)	27.2 (24.4 – 29.5)	0.67
Education			
< High school	27 (7.4)	30 (8.1)	0.13
High school graduate	71 (19.5)	83 (22.5)	
Some college or vocational training	108 (29.7)	131 (35.5)	
College graduate	66 (18.1)	54 (14.6)	
Postgraduate	91 (25.0)	71 (19.2)	
Smoking status			
Never	160 (44.0)	95 (25.6)	<0.0001
Former	169 (46.4)	217 (58.8)	
Current	35 (9.6)	57 (15.5)	
Hours spent in vigorous activity			
none	40 (11.0)	55 (14.9)	0.16
3 hours/week	204 (56.0)	193 (52.3)	
4 hours/week	96 (26.4)	89 (24.1)	
Family history of bladder cancer	6 (1.7)	7 (1.9)	0.71
Personal history of diabetes	30 (8.2)	33 (8.9)	0.73
Regular aspirin use	180 (49.5)	207 (56.1)	0.08
Regular ibuprofen use	85 (22.4)	108 (29.3)	0.07
Dietary and supplement intake (per day)			
Total energy (kcal)	2,162 (1,628 – 2,656)	2,091 (1,520 – 2,665)	0.32
Vitamin D (µg)	4.9 (3.4 – 7.6)	4.8 (3.2 – 7.1)	0.32
Calcium (mg)	905 (682 – 1,266)	894 (606 – 1,188)	0.14
Dairy food (My Pyramid cup equivalents)	1.7 (1.1 – 2.5)	1.5 (0.9 – 2.3)	0.01
Red meat (g)	68.5 (41.4 – 115.0)	78.2 (43.3 – 121.9)	0.26
Supplemental vitamin D (µg)	0 (0 – 10.0)	0 (0 – 10.0)	0.87
Supplemental calcium (mg)	0 (0 – 162)	0 (0 – 162)	0.96
Supplemental vitamin E (mg)	13.5 (0 – 180)	13.5 (0 – 104)	0.67
Serum 25(OH)D (nmol/L)	53.6 (39.5 – 68.1)	52.4 (39.6 – 65.8)	0.59
Serum DBP (µg/mL)	237 (186 – 295)	232 (189 – 290)	0.68

Table 2

Odds ratios and 95% confidence intervals of baseline serum 25(OH)D and bladder cancer risk, PLCO

	# Cases	# Controls	OR (95% CI) ^a	OR (95% CI) ^b	OR (95% CI) ^c
25(OH)D (nmol/L)					
<25	16	17	0.86 (0.38 – 1.94)	0.73 (0.29 – 1.84)	0.74 (0.29 – 1.87)
25 - <37.5	54	63	0.75 (0.47 – 1.20)	0.71 (0.42 – 1.19)	0.72 (0.43 – 1.23)
37.5 - <50	92	76	1.10 (0.75 – 1.63)	1.17 (0.76 – 1.80)	1.17 (0.76 – 1.80)
50 - <75	158	144	1.0 (ref)	1.0 (ref)	1.0 (ref)
75	49	64	0.71 (0.46 – 1.09)	0.85 (0.53 – 1.35)	0.85 (0.53 – 1.38)
<i>p for trend^d</i>			0.50	0.97	0.99
Season-specific quartiles^e of 25(OH)D					
1	84	100	1.00 (0.65 – 1.52)	0.84 (0.52 – 1.36)	0.84 (0.51 – 1.38)
2	101	81	1.43 (0.96 – 2.13)	1.24 (0.80 – 1.92)	1.24 (0.79 – 1.93)
3	103	82	1.49 (1.00 – 2.21)	1.29 (0.84 – 1.99)	1.28 (0.83 – 1.98)
4	81	101	1.0 (ref)	1.0 (ref)	1.0 (ref)
<i>p for trend^f</i>			0.95	0.56	0.58
Residual-adjusted quartiles^g of 25(OH)D					
1	93	90	1.19 (0.78 – 1.83)	1.01 (0.53 – 1.64)	1.04 (0.63 – 1.71)
2	91	92	1.15 (0.77 – 1.70)	1.11 (0.72 – 1.71)	1.12 (0.72 – 1.74)
3	100	83	1.39 (0.91 – 2.12)	1.13 (0.71 – 1.81)	1.13 (0.70 – 1.82)
4	85	99	1.0 (ref)	1.0 (ref)	1.0 (ref)
<i>p for trend^f</i>			0.61	0.94	0.88
DBP (µg/mL)					
Q1: <187	90	92	1.0 (ref)	1.0 (ref)	1.0 (ref)
Q2: 187 - <235	98	86	1.03 (0.67 – 1.58)	0.80 (0.50 – 1.29)	0.79 (0.49 – 1.28)
Q3: 235 - <291	91	92	1.18 (0.78 – 1.78)	1.12 (0.71 – 1.76)	1.08 (0.68 – 1.71)
Q4: ≥291	90	94	1.03 (0.67 – 1.56)	0.90 (0.57 – 1.42)	0.85 (0.53 – 1.36)
<i>p for trend^d</i>			0.71	0.61	0.58
25(OH)D:DBP molar ratio					
Q1: <9.6	87	90	1.0 (ref)	1.0 (ref)	-

	# Cases	# Controls	OR (95% CI) ^a	OR (95% CI) ^b	OR (95% CI) ^c
Q2: 9.6 - <13.0	103	89	0.86 (0.54 - 1.36)	0.88 (0.53 - 1.48)	-
Q3: 13.0 - <17.2	79	95	1.00 (0.66 - 1.50)	1.02 (0.65 - 1.60)	-
Q4: 17.2	100	90	0.75 (0.49 - 1.15)	0.82 (0.51 - 1.32)	-
<i>p for trend^d</i>			0.83	0.90	

^aConditioned on the matching factors.

^bConditioned on the matching factors. Further adjusted for smoking status, pack-years of smoking, dairy consumption, and use of aspirin or ibuprofen.

^cConditioned on the matching factors. Further adjusted for smoking status, pack-years of smoking, dairy consumption, use of aspirin or ibuprofen, and mutually adjusted for 25(OH)D and vitamin D binding protein.

^dMedian of each category modeled as a continuous variable.

^eWinter quartile cutpoints (in nmol/L) = Q1: <35, Q2: 35 - <49, Q3: 49 - <66, Q4: 66; summer quartile cutpoints (in nmol/L) = Q1: <48, Q2: 48 - <60, Q3: 60 - <73, Q4: 73

^fOrdinal variable for quartile group modeled as a continuous variable.

^gCutpoints for residual-adjusted quartiles were Q1: < 54.5, Q2: 54.5 - < 54.8, Q3: 54.8 - <55.0, Q4: 55.0, created by calculating residuals from the regression line of log transformed 25(OH)D against calendar week of blood collection and adding them to the mean 25(OH)D level.